Journal of
Cardiology & Cardiovascular
Surgery

Original Article

DOI: 10.51271/JCCVS-0048

The effect of ranolazine on erectile dysfunction in coronary artery disease patients

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Cite this article: Turgay Yıldırım Ö, Aydın F, Akşit E, Hüseyinoğlu Aydın A, Dişikırık T, Özgeyik M. The effect of ranolazine on erectile dysfunction in coronary artery disease patients. *J Cardiol Cardiovasc Surg.* 2025;3(1):5-9.

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Received: 24/01/2025 ◆ **Accepted**: 17/03/2025 ◆ **Published**: 27/03/2025

ABSTRACT

Aims: Erectile dysfunction (ED) and coronary artery disease (CAD) are disorders with similar pathophysiology and the prevalence of ED may be as high as 75% in cardiovascular patients. Ranolazine is a second line therapy in CAD patients with angina. It inhibits the late sodium current in cardiomyocytes. It also has positive effects on endothelial dysfunction which is a common disruption on both CAD and ED. We aim to evaluate the effect of ranolazine on ED in CAD patients with angina complaints.

Methods: A total of 37 CAD patients were included for the study. Ranolazine was started to patients with angina symptoms. Sexual Health Inventory for men (SHIM) questionnaire was used to evaluate the status of ED. The questionnaire was applied to patients before the start and at the 6th month of ranolazine treatment.

Results: The SHIM scores of each question did not change significantly after the follow up period (p>0.05). The total SHIM score at the beginning was 10.7±5.4 and after 6 months the SHIM score was 10.7±6.3 and the difference was statistically insignificant (p=0.757). The changes in the SHIM classes were not statistically significant (p=0.454).

Conclusion: Ranolazine does not have positive or negative effects on ED at CAD patients with angina pectoris. Further studies with larger patient population must be done to confirm the results of the study.

Keywords: Coronary artery disease, erectile dysfunction, ranolazine, Sexual Health Inventory for men questionnaire

INTRODUCTION

Erectile dysfunction (ED) is defined as an inadequate penile erection or inability to sustain an erection that causes dissatisfaction during sexual intercourse.[1] Etiology behind ED may be explained by psychogenic, neurogenic, hormonal, drug-induced, vasculogenic and lifestyle factors or systemic disorders.[2] Cardiovascular diseases and ED have similar risk factors like age, diabetes mellitus, insulin resistance, hypertension, smoking, total cholesterol, low density lipoprotein cholesterol levels and high body-mass index.[3] The prevalence of ED in coronary artery disease (CAD) patients can be as high as 75%.[4,5] The pathophysiology under ED and CAD is also similar. Endothelial dysfunction, chronic inflammation and the artery size hypothesis are used to explain the mechanism underneath.[6,7] Many drugs are used for the treatment of CAD patients which also have effects on ED. Thiazide diuretics and most beta blockers have negative effects while vasodilator beta blockers, calcium antagonists have neutral impact and nebivolol has positive impact on ED. Adjusting the treatment of the patients may improve the problem because cardiac patients already have a tendency for ED and many drugs worsen the underlying situation.[8-10]

Ranolazine is a second line antianginal therapy for CAD patients.[10] Ranolazine selectively inhibits the late sodium current in cardiomyocytes. It reduces intracellular calcium overload and increase the oxygen consumption.[11] Ranolazine also has anti-inflammatory and antioxidant effects which may be important for microvascular angina.[12] ED was thought to be a psychogenic disorder since late 20th century but now it is recognized as a physiologic disorder affecting the penile circulation.[13,14] The artery size hypothesis states that atherosclerosis affects all major vascular beds but smaller vascular beds like penile artery will be affected earlier compared to coronary artery which are larger in diameter and will tolerate atherosclerosis at an extent. But all major arteries will be effected to the same extend in the end.[5,7] The effects of ranolazine on endothelium and vascular bed may improve the disruptions on penile tissue since both ED and CAD has similar mechanism and ranolazine effects the tissues by several ways and improves endothelial function and electrolyte disruptions.[15,16]

While ranolazine's primary mechanism of action involves the inhibition of the late sodium current in cardiomyocytes,

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leading to reduced intracellular calcium overload and improved myocardial relaxation[11], its potential effects on penile function remain unclear. Unlike cardiac tissue, the penile nerve conduction system and vascular regulation rely on a complex neurovascular coupling mechanism, with nitric oxide (NO) playing a central role in smooth muscle relaxation and penile erection.[13,14] Ranolazine has been shown to enhance endothelial nitric oxide synthase (eNOS) activity and reduce oxidative stress in peripheral vascular beds, which could theoretically improve penile blood flow and smooth muscle relaxation.[15,16] However, the physiological differences between cardiac and penile tissues, particularly in terms of nerve conduction and vascular demands, may limit the direct applicability of ranolazine's effects. This study aims to explore whether ranolazine's systemic vascular and endothelial benefits can translate into improvements in erectile function in CAD patients.

METHODS

The study was conducted with the permission of Eskişehir Osmangazi University Non-interventional Clinical Researches Ethics Committee (Date: 18.09.2018, Decision No: 12) and patients provided written informed consent. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The patient population was selected from 200 male patients with angina complaints who were admitted to the cardiology outpatient clinic between 15.11.2018 and 30.04.2019. These patients had CAD proven by coronary angiography and extended-release ranolazine treatment was needed to be started for angina pectoris. Patients under 18 years old, patients without sexual partners, patients who use phosphodiesterase inhibitors, patients whom the ranolazine use in not recommended were not included. After excluding those patients who did not agree to participate in the study, did not show up for their follow-up examination, and had irreversible ED due to urological reasons (eg. trauma), the remaining 37 people were included in the study.

The Sexual Health Inventory for men (SHIM) questionnaire was used for the evaluation of ED. The questionnaire consists of five questions. The scores changes between 1 to 25. According to the scores of the questionnaire, ED was classified into 5 categories. The scores between 1-7 represents "severe ED", 8-11 represents moderate ED, 12-16 represents mild to moderate ED, 17-21 represents mild ED and 22-25 represents no ED.[17] This questionnaire was administered to CAD patients before the ranolazine treatment and 6 months after the beginning of ranolazine treatment. The questions and appointed scores are shown in **Table 1**.

This study was designed prospectively. Ranolazine 500 mg twice a day was started in all patients participating in the study. SHIM questionaire was applied before treatment was initiated. After 6 months of follow-up, SHIM questionnaire was applied to patients who still continued to use ranolazine 500 mg twice a day.

Statistical Analysis

Data are presented as mean±standard deviation (SD) and as proportions for categorical variables. Distribution of the data for normality was tested by the Shapiro–Wilk test and homogeneity of group variances were tested by the Levene test. SHIM scores and comparison between SHIM categories are evaluated by Wilcoxon signed rank test. $p<0.05$ was considered to be statistically significant. The data were analyzed using SPSS 20.0 (IBM SPSS Ver. 20.0, IBM Corp, Armonk NY, USA).

Table 1. The Sexual Health Inventory for Men (SHIM) questionnaire

How do you rate your confidence that you could get and keep an erection?	Very low: 1 Low: 2 Moderate: 3 High: 4 Very high: 5
When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No sexual activity: 0 Almost never or never: 1 A few times (much less than half the time): 2 Sometimes (about half the time): 3 Most times (much more than half the time): 4 Almost always or always: 5
During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did not attempt intercourse: 0 Almost never or never: 1 A few times (much less than half the time): 2 Sometimes (about half the time): 3 Most times (much more than half the time): 4 Almost always or always: 5
During sexual intercourse, how difficult was it to maintain your erection until completion of intercourse?	Did not attempt intercourse: 0 Extremely difficult: 1 Very difficult: 2 Difficult: 3 Slightly difficult: 4 Not difficult: 5
When you attempted sexual intercourse, how often was it satisfactory for you?	Did not attempt intercourse: 0 Almost never or never: 1 A few times (much less than half the time): 2 Sometimes (about half the time): 3 Most times (much more than half the time): 4 Almost always or always: 5

RESULTS

A total of 37 CAD patients were included in the study. Mean age of study population was 60.6±8.9. 70.3% of the patients (n=26) had hypertension and 35.1% had diabetes mellitus. The ejection fraction value was 58.6±5.9 and mean NYHA class of the patients were 1.3±0.5. Atrial fibrillation patients constituted 8.1% (n=3) of the sample and mean heart rate of these patients was 77.5±3.5 bpm. Remaining 91.9% of the patients had sinus rhythm with a mean heart rate of 69.5±7.5 bpm. The medications of the patients were given at **Table 2**.

At the beginning of the study; 35.3% (n=12) of the patients had severe ED, 2.9% (n=1) had moderate ED, 47.1% (n=16) had mild to moderate ED and 14.7% (n=5) had mild ED. After 6 months use of ranolazine; 35.3% (n=12) of the patients had severe ED, 17.6% (n=6) had moderate ED, 29.4% (n=10) had mild to moderate ED, 11.8% (n=4) had mild ED and 5.9% (n=2) of the patients had no ED. The changes in the SHIM classification groups were not statistically significant (p=0.454). 8.1% (n=3) of ED patients' SHIM classes were progressed and 16.2% (n=6) of the patients classes were regressed after 6 months of treatment. The remaining 75.7% of the sample remained in the same class.

The SHIM scores of each question did not change significantly after the follow up period (p>0.05). The total SHIM score at the beginning was 10.7±5.4 (**Figure 1**) and after 6 months the SHIM score was 10.7±6.3 (**Figure 2**). The change was not statistically significant (p=757). The changes in the scores

Table 2. Baseline characteristics of the study population

Age, years	60.6±8.9
Hypertension	26 (70.3%)
Diabetes mellitus	13 (35.1%)
Electrocardiography	34 (91.9%) sinus rhythm 3 (8.1%) atrial fibrillation
Ejection fraction	58.6±5.9
New York Heart Association classification	1.3±0.5
Ranolazine dose	473.0±52.2
Beta blockers	27 (73.0%)
Calcium channel blockers	4 (10.8%)
ACEIs	16 (43.2%)
ARBs	8 (21.6%)
Spironolactone	4 (10.8%)
Thiazide diuretics	10 (27.0%)
Other diuretics (Indapamide, furosemide)	15 (40.5%)
Digoxin	1 (2.7%)
ASA	23 (62.2%)
Anticoagulant	3 (8.1%)
P2Y12 inhibitors	6 (16.2%)
Statin	23 (62.2%)

Data are expressed as mean±standart deviation or number (%), ACEIs: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blockers, ASA: Acetylsalicylic acid

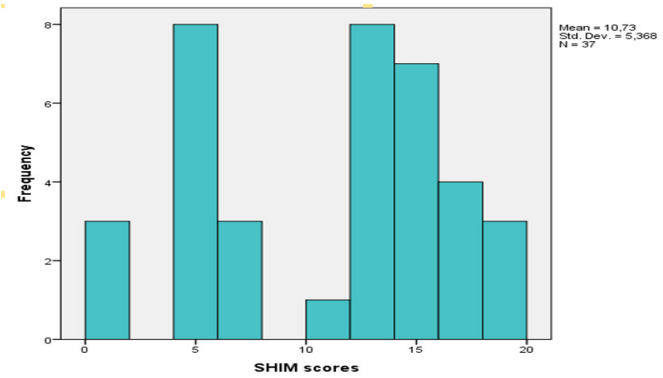

Figure 1. The total SHIM score of the patients at the beginning of the ranolazine treatment
SHIM: The Sexual Inventory for men

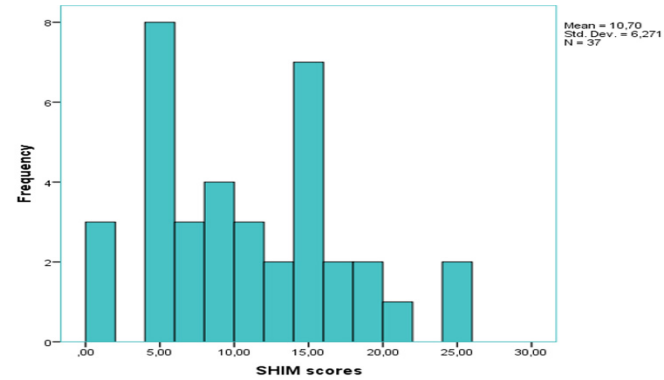

Figure 2. The total SHIM score of the patients at the 6th month of the ranolazine treatment
SHIM: The Sexual Inventory for men

were given at **Table 3**. The individual changes of patients at the SHIM score are given in **Figure 3**.

DISCUSSION

We studied the effect of ranolazine by using SHIM score at the beginning and at the sixth month of treatment. Our study revealed that ranolazine has no statistically significant positive or negative effect on ED at CAD patients.

Table 3. Changes at SHIM score results after ranolazine use

	Before use	6th month	p
Question 1	2.2 ± 0,9	2.2±1.1	0.873
Question 2	2.0±1.1	2.0±1.3	0.967
Question 3	2.1±1.2	2.1±1.3	0.874
Question 4	2.2±1.4	2.2±1.2	0.791
Question 5	2.2±1.2	2.2±1.4	0.608
Total SHIM score	10.7±5.4	10.7±6.3	0.757
ED classification*	2.3±1.1	2.3±1.2	0.454

*The classification according to the SHIM scores. The scores of 1-7 represents severe ED (group 1), 8-11 represents moderate ED (group 2), 12-16 represents mild to moderate ED (group 3), 17-21 represents mid ED (group 4) and 22-25 represents no ED (group 5). ED: Erectile dysfunction, SHIM: The Sexual Inventory for men

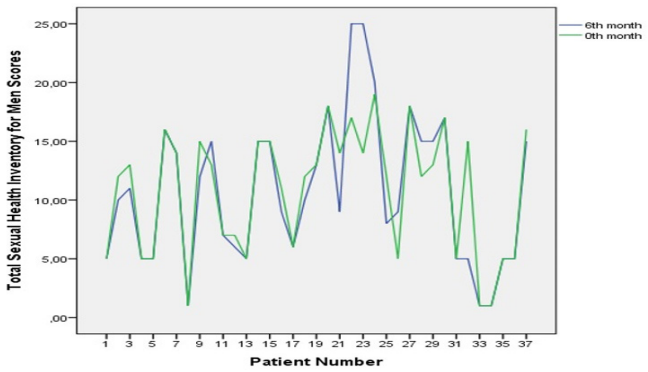

Figure 3. Individual changes in the SHIM scores after ranolazine treatment
SHIM: The Sexual Inventory for men

CAD and ED coexist in patients due to similar pathophysiological mechanisms. Patients with cardiac diseases have a probability of 39% to have ED.[18] One of the major mechanisms under these disorders is endothelial dysfunction.[19] Endothelial dysfunction affects the arteriolar system and disturbs relaxation and prevents vasodilatation in ED patients.[20] Diabetes mellitus, hypercholesterolemia also affects endothelium and both disorders lies as a risk factor on both ED and CAD. These disorders cause smooth muscle cell degradation and disrupt vasodilatation and causes ED.[20,21] Preservation of endothelial dysfunction can restore normal function in patients with atherosclerosis. Baumhakel et al.[22] showed that ivabradin has a positive effect on endothelial function at corpora cavernosa in mice on high fat diet. High fat diet was used to disrupt the normal endothelial function and ivabradin improved the penile endothelial function after 3 months of treatment. Ivabradin reduced penile fibrosis and oxidative stress and by doing so improvement at endothelial function occurred. Ranolazine also has positive effect on endothelial dysfunction.[23] Deshmukh et al.[21] showed that ranolazine improves endothelial dependent vasodilatation and improves endothelial function within 6 weeks at patents with CAD. The previous studies suggested that ranolazine which also have positive effects on endothelial function may regulate disrupted endothelial function at penile endothelium and improve ED. Penile erection is a complex process involving hormonal, psychological, and neurovascular mechanisms. NO plays a central role in this process by activating guanylate cyclase, increasing cyclic GMP levels, and reducing intracellular calcium concentrations, which ultimately relaxes smooth muscle cells in the penile vasculature.[13,14] Ranolazine has been shown to enhance eNOS activity and reduce oxidative stress in peripheral vascular beds.[15,16] These effects suggest that ranolazine could theoretically improve endothelial function and penile

blood flow, which are critical for erectile function. However, the penile vasculature and nerve conduction system differ significantly from the cardiac conduction system. Unlike cardiac tissue, penile tissue relies heavily on neurovascular coupling, where the interaction between cavernous nerves and endothelial cells is essential for smooth muscle relaxation and blood flow regulation. Ranolazine's effects on sodium and calcium channels may not directly influence these processes, which could explain the lack of significant improvement in ED observed in our study.[21-24] Although 90% of the patients who participated in our study had increased effort capacity and the angina complaints were regressed, we failed to prove that ranolazine has positive effect on ED in atherosclerotic patients.

Penile erection is regulated by hormonal and psychological events.[24] With the effect of sexual stimulation, neurotransmitters and relaxing factors are released from cavernous nerve terminals and endothelial cells of the penis. This events cause smooth muscle relaxation at the penile arterioles and arteries and blood flow increases causing penile erection. Endothelial cells and neural tissue secrete NO and by this event muscle relaxation occurs.[25] Ranolazine also increases NO production and decrease NO degradation by inhibiting receptors on endothelial cells by mediating late sodium channel current.[26,27] The positive effect of ranolazine on NO concentration may have a positive effect on ED. Because NO increases intracellular concentration of cyclic GMP which eventually decreases calcium concentrations and relaxes smooth muscle of corpus cavernosum.[25] Even though the mechanisms suggested otherwise we observed no positive effects of ranolazine on ED. There are many causes under ED like psychogenic, neurogenic, hormonal, drug-induced, vasculogenic and lifestyle factors or systemic disorders.[2] Even though there were no changes in cardiac medication, the patients may fail to inform us about other medications they use during the 6 months period of ranolazine treatment.

Limitations

There are many limitations in our study. First of all we did not evaluate psychogenic factors that may cause ED in our study. We also evaluate the status of ED by using SHIM questionnaire. The patients may answer subjectively to the questions because patients may be sensitive to the topic compared to other disorders. The results may be more objective if we used penile Doppler ultrasound instead. Also the number of patients was low which was a major limitation of the study.

CONCLUSION

We evaluated the effect of ranolazine on ED by using SHIM scoring at patient with CAD. We found out that ranolazine may not have positive or negative effects on patients with ED.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Eskişehir Osmangazi University Non-interventional Clinical Researches Ethics Committee (Date: 18.09.2018, Decision No: 12).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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